

# METHOD FOR THE LONG TERM REDUCTION OF BODY FAT STORES, INSULIN RESISTANCE, HYPERINSULINEMIA AND HYPERGLYCEMIA IN VERTEBRATES

## RELATED APPLICATIONS

This invention is a continuation-in-part of copending U.S. application Ser. No. 463,327, filed Jan. 10, 1990 by Anthony H. Cincotta and Albert H. Meier.

## FIELD OF THE INVENTION

This invention relates to an improved process for the reduction in vertebrates, animals or humans, of body fat stores, and reduction of insulin resistance, hyperinsulinemia, which is often associated with insulin resistance, and hyperglycemia, or reduction of plasma glucose. In particular, it relates to a process requiring the timed daily administrations of a dopamine agonist and a prolactin stimulator at appropriate preselected times of day, and preferably also a thyroid hormone, to reduce and control over an extended period the stated pathologies which, with obesity, are pathologies characteristic of the onset of noninsulin dependent, or Type II diabetes.

## BACKGROUND

In U.S. Pat. No. 4,659,715, which issued Apr. 21, 1987 to Albert H. Meier and Anthony H. Cincotta, there is disclosed a method for the reduction in vertebrate animals of body fat stores, without concomitant decrease in muscle mass, via the administration of multiple daily doses over prescribed periods of a prolactin-inhibiting, or dopamine compound. This method, which is associated with an altered lipid metabolism, offers hope to those suffering with obesity; a serious world-wide health problem.

In pending U.S. application Ser. No. 463,327, supra, there is disclosed a method, or process, for the long term modification and regulation of lipid metabolism in a vertebrate, animal or human, not only to reduce obesity, but also to reduce insulin resistance, and hyperinsulinemia or hyperglycemia, or both, by administration to a subject of a prolactin-inhibiting compound, or dopamine agonist. The role of prolactin in a vertebrate species to control these pathologies (the hallmarks of noninsulin dependent, or Type II diabetes), it was found, was crucial! The level of prolactin in the blood of a species is time-of-day dependent, and cyclic, its level in the blood rising and falling at different times of day dependent on the amount of fat deposited in the body of the subject. The phase relationships between the rise and fall of prolactin which appears in the blood streams of obese and lean subjects, respectively, are different. Administration of the dopamine agonist, it is disclosed, is made over a limited period at a time of day dependent on the normal circadian rhythm of fat and lean members, respectively, of a similar species based on the result to be achieved. Where, e.g., it is desired to reduce the body fat of a subject, decreases in body fat deposits are produced by treatment of the obese species on a timed daily sequence based on circadian rhythms of the peak prolactin, or peak prolactin and peak glucocorticosteroid, blood level established for lean members of a similar species. A person, whether lean or obese, showing the effects of insulin resistance, or hyperinsulinemia and/or hyperglycemia, or both insulin resistance and hyperinsulinemia and/or hyperglycemia, treated

with the dopamine agonist or prolactin-inhibiting compound, in the same manner as a person suffering with obesity, it was found would become more sensitive to insulin, and the effects of hyperinsulinemia and/or hyperglycemia would be reduced on a long term basis. Thus, insulin resistance, and hyperinsulinemia or hyperglycemia, or both, like obesity, can be controlled in humans on a long term basis by treatments corresponding to that for the treatment of obesity to lower fat deposits in the body of the subject.

Albeit the administration to obese subjects of a prolactin-inhibiting compound on a time-of-day schedule related to a daily prolactin secretion cycle mimicking that of a lean subject to cause the obese subject to lose body fat, the results have proven less than 100 percent effective. For example, in treating a large population of obese subjects to reduce body fat during the winter months, a significant reduction in body fat occurred in the majority of the treated patients. On the other hand, it was observed that a lower percentage of a population of obese patients similarly treated during the summer months showed a significant reduction in body fat. This suggests that prolactin secretions in a subject are to some extent seasonal, but equally if not more important it suggests that better timing and control of prolactin secretions in a subject, particularly during the summer months, can improve and render more effective the liporegulatory nature of the treatments to reduce obesity, reduce insulin resistance, and hyperinsulinemia or hyperglycemia, or both.

## OBJECTS

It is, accordingly, a primary objective of this invention to provide further improvements in a method for the long term modification and regulation of lipid metabolism to alter, phase shift and reset on a long term, or permanent basis, circadian hormonal timing mechanisms in the neural centers of the brain.

In particular, it is an object to provide a process for resetting the circadian neural center of vertebrate animals, including humans, to alter neural centers which stimulate and control prolactin secretion to produce long lasting changes in the amount of body fat stores, the sensitivity of the cellular response of a species to insulin, and overcome hyperinsulinemia and/or hyperglycemia, which generally accompanies insulin resistance.

A more specific object is to provide a process for resetting the circadian neural centers of animals, including humans, which regulate and control lipogenesis to decrease obesity and maintain the more normal body fat stores of a lean animal, or lean human, on a long term basis.

A further, and equally specific object is to provide a process for resetting on a long term basis the circadian neural centers, particularly in humans, which regulate and control the sensitivity and responsiveness of the cells to insulin, and suppress hyperinsulinemia or hyperglycemia, or both.

## THE INVENTION

These objects and others are achieved in accordance with this invention, a process which embodies in addition to the administration of a dopamine agonist, e.g. L-DOPA or bromocriptine, on a timed daily basis to modify and reset the neural circadian oscillation expressed by the prolactin rhythm (prolactin oscillation)